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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MOHAMMAD SARWAR NASIR and MICHAEL E. JOLLEY

Appeal 2008-1765
Application 09/905,452
Technology Center 1600

Decided: March 27, 2008

Before DONALD E. ADAMS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for detecting aflatoxins which the Examiner has rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Background

"Aflatoxins are mycotoxins produced by *Aspergillus flavus* molds" (Spec. 2). The Specification notes that "[v]arious forms of aflatoxin, including B1, B2, G1, and G2 and many others, have been found in many

forms of human foods, such as cereals, grains and peanut products" (Spec. 2). According to the Specification, "various analytical methods have been devised to quantitatively determine the amount of aflatoxin in agricultural products" (Spec. 2).

Appellants teach a

> homogeneous assay for the determination of aflatoxins in agricultural products. Aflatoxin is extracted from a sample, and the extract is combined with a tracer and an antibody to provide a mixture. The antibody is specific for aflatoxin. The tracer comprises an aflatoxin oxime conjugated to a fluorophore. The tracer is able to bind to the antibody to produce a detectable change in fluorescence polarization. The fluorescence polarization of the mixture is measured and compared to a standard curve.

(Spec. 3.)

Statement of the Case

The Claims

Claims 1-18 are on appeal. We will focus on claims 1 and 11, which are representative and read as follows:

> 1. A homogeneous assay for the determination of aflatoxins in agricultural products, said homogeneous assay comprising the steps of:
>
> extracting aflatoxin from a sample to provide an extract;
>
> combining said extract with a tracer and an antibody to provide a mixture, said antibody being specific for aflatoxin, said tracer comprising an aflatoxin oxime conjugated to a fluorophore, said tracer being able to bind to said antibody to produce a detectable change in fluorescence polarization;
>
> measuring the fluorescence polarization of said mixture to obtain a measured fluorescence polarization; and

comparing said measured fluorescence polarization with a characterized fluorescence polarization value, said characterized fluorescence polarization value corresponding to a known aflatoxin concentration.

11. An assay kit for the determination of aflatoxins in agricultural products in a homogeneous assay, said assay kit comprising:

an antibody and a tracer, each in an amount suitable for at least one assay, and suitable packaging, said antibody being specific for aflatoxin, said tracer comprising an aflatoxin oxime conjugated to a fluorophore, said tracer being able to bind to said antibody to produce a detectable change in fluorescence polarization in a homogeneous assay.

The prior art

The Examiner relies on the following prior art reference to show unpatentability:

Dixon	US 4,835,100	May 30, 1989
McMahon	US 5,166,078	Nov. 24, 1992
Michel	US 5,741,654	Apr. 21, 1998

Nasir et al., "Fluorescence Polarization: An Analytical Tool for Immunoassay and Drug Discovery", 2 *Combinatorial Chemistry & High Throughput Screening* 177-90 (1999).

The issues

The rejections as presented by the Examiner are as follows:

Claims 1-4, 8 and 11-18 stand rejected under 35 U.S.C. § 103(a), as being obvious over Dixon and Nasir.

Claims 5-7 stand rejected under 35 U.S.C. § 103(a), as being obvious over Dixon, Nasir, and Michel.

Claims 9-10 stand rejected under 35 U.S.C. § 103(a), as being obvious over Dixon, Nasir, and McMahon.

35 U.S.C. § 103(a) rejection over Dixon and Nasir

The Examiner argues that

> Nasir alone suggests independent claims 1 and 11 by teaching a Fluorescence Polarization assay for detection of Mycotoxins, which is a form of aflatoxins. And since aflatoxins ha[ve] to first be converted to an aflatoxin oxime before being conjugated to a label, Nasir would have had to perform this method before detection of aflatoxins using the method of Fluorescence Polarization.

(Ans. 7-8.)

The Examiner argues that "Dixon was combined with Nasir because Dixon actually taught detection of aflatoxin oxime with an ELISA assay" (Ans. 8). The Examiner also argues that "Nasir would have a reasonable expectation of success in modifying the reference of Dixon to include detection of aflatoxins utilizing a fluorescence polarization assay" (Ans. 9). The Examiner concludes "one of ordinary skill in the art would have wanted to detect toxins in grain, namely aflatoxins using FP because it offers sensitive results that can be obtained rapidly without any separation and purification steps" (Ans. 10).

Appellants argue that

> the Dixon/Nasir combination fails to teach or suggest either of the following: a 'tracer comprising an aflatoxin oxime conjugated to a fluorophore' as recited in independent claims 1 and 11; and 'said tracer being able to bind to said antibody to produce a detectable change in fluorescence polarization' as recited in claims 1 and 11.

(App. Br. 3.)

Appellants further contend that "the HRP enzyme label is chemically and functionally very different from a fluorophore label" (App. Br. 4). Appellants argue that "replacing the HRP label in Dixon with a fluorophore would change the principle of operation set forth in Dixon" (App. Br. 5). Appellants also argue that "[e]ven if the statements in Nasir regarding mycotoxin research could be applied to aflatoxin specifically, the statements actually teach away from conjugating aflatoxin oxime with a fluorophore" (App. Br. 6).

In addition, Appellants argue that "Nasir does not teach one of ordinary skill in the art whether an aflatoxin-based tracer would actually produce a detectable change in fluorescence polarization upon binding to a specific antibody or whether it would suffer from the 'propeller effect.'" (App. Br. 9). (The "propeller effect" is "used to describe the phenomenon whereby, although binding has occurred, little polarization shift is observed. This is caused by the uncoupling of the fluorophore and binding site due to a long, flexible linkage" (Nasir 180, col. 2)).

In view of these conflicting positions, we frame the obviousness issues before us as follows:

Whether it would have been obvious to a person of ordinary skill to apply the fluorescence polarization immunoassay method of Nasir to the detection of aflatoxin taught by Dixon using an aflatoxin oxime?

Findings of Fact

1. Nasir teaches "[i]n view of the involvement of various mycotoxins in human, animal and grain diseases, rapid and cheaper field tests for the determination of these mycotoxins are becoming an urgent need" (Nasir 181, col. 2).

2. Nasir teaches that fluorescence polarization, "with its latest developments in simple and relatively inexpensive instrumentation, is a technique of great potential in this area of research" (Nasir 182, col. 1).

3. Nasir teaches that a "mycotoxin antigen of interest is labeled with a suitable fluorescent molecule (tracer)" (Nasir 182, col. 1).

4. Nasir teaches that "[m]ycotoxin is extracted from grains with a suitable solvent and the sample is added into the antibody solution." (Nasir 182, col. 1.)

5. Nasir teaches that "[t]racer is added and its fluorescence polarization is measured, which is inversely related to the amount of free mycotoxin" (Nasir 182, col. 1).

6. Nasir teaches that

> An antigen or its derivative is labeled with a fluorescent molecule and the polarization is measured. Upon reacting with a specific antibody for the antigen, the polarization increases. Depending upon the quantity of unlabeled antigen in the sample, a competition occurs between the fluorescent-labeled and unlabeled antigen and the polarization decreases accordingly. Thus the observed polarization is correlated with the antigen concentration in the unknown sample [Fig. (5)] [References omitted]. An optimum antibody-labeled antigen sample ratio is important for these studies to obtain the desired standard curve.

(Nasir 181, col. 2.)

7. Nasir discloses that the tracer method for toxin detection was successfully performed on at least three different toxins by Dasgupta, Rogers and Eremin (*see* Nasir 182, col. 1).

8. Nasir teaches a motivation to use fluorescence polarization, noting that it

> is a powerful but simple technique for routine, in house and field diagnostic applications for . . . detection of . . . grain mycotoxins and environmental monitoring of pesticides. . . . The reactions are homogeneous, rapid and single step and require only one or two reagents beside the sample. Most of the reagents are very stable and the results are independent of intensity. Results are fast, accurate and free of contamination problems. Because only a few reagents are required, the assays are easy to develop and reagents can be stored easily. Instruments are relatively inexpensive, stable and suitable for field testing and automation. There are no washing steps, and the assays tolerate the use of relatively impure receptors, cloudy and colored solutions. . . . These features make fluorescence polarization a useful adjunct to existing methodologies due to its ease of use, sensitivity, speed and cost effectiveness.

(Nasir 186, col. 2.)

9. Dixon teaches that "[i]nterest in development of rapid sensitive assays for detection of aflatoxins has been steadily increasing, since the compounds are known to occur naturally in peanuts, corn, milk, wheat, and animal rations" (Dixon 1:31-34). The skilled artisan knows that aflatoxin is a mycotoxin; i.e., a toxin produced by fungi (*see* Dixon 1:25-27).

10. Dixon teaches "a highly specific and sensitive assay method and test kit for aflatoxin B_1 and G_1 using novel monoclonal antibodies"

(Dixon 2:33-35). Dixon further teaches that detection was perfromed using ELISA (Dixon 5:32-6:44).

11. Dixon teaches that "[s]ince aflatoxin B_1 possesses no reactive groups for conjugation, it was first converted to aflatoxin- B_1-carboxymethylamine (aflatoxin B_1-oxime)" (Dixon 4:66-68).

12. Dixon teaches that the converted aflatoxin B_1-oxime was "conjugated to BSA or OA (fraction VII) by the N-hydroxysuccinimide procedure" (Dixon 5:3-5).

Discussion of 35 U.S.C. § 103(a) over Nasir and Dixon

Nasir teaches the detection of mycotoxins in agricultural products using a homogenous fluorescence polarization assay (FF 1-8). In particular, Nasir teaches extracting the mycotoxin from a sample of grains (FF 4). Nasir teaches forming a tracer of the mycotoxin and a fluorescent label, and combining the extracted mycotoxin with the tracer and an antibody (FF 3-5). Nasir then teaches measurement of the fluorescence polarization and comparing that to a characterized value to determine the concentration of the mycotoxin in the grain sample (FF 5-6). Nasir teaches that at least three tested toxins were successfully detected by fluorescence polarization (FF 7). In addition, Nasir provides the motivation to apply fluorescence polarization to mycotoxins, including ease of use, sensitivity, speed, and cost effectiveness (*see* FF 8).

The Examiner acknowledges that Nasir does not teach the species of aflatoxin in the genus of mycotoxins (Ans. 7). The Examiner relies upon Dixon for the disclosure that aflatoxin is a mycotoxin of interest which is found in agricultural products and detectable by immunodetection (*see* FF 9-

10). Since Nasir does not teach the conjugation of aflatoxins, Dixon is also relied upon to show that in order to conjugate to an aflatoxin, the aflatoxin must first be converted to aflatoxin- B_1-carboxymethylamine (aflatoxin B_1-oxime) (*see* FF 11-12).

The obviousness case rests on whether a person of ordinary skill in the art would have considered it obvious to form a fluorescently labeled tracer with aflatoxin B_1 in a method of performing fluorescence polarization on aflatoxin. Dixon teaches that, since aflatoxin B_1 possesses no reactive groups for conjugation, it would have been necessary to convert aflatoxin B_1 to aflatoxin B_1-oxime before it could have been conjugated to a fluorophore (*see* FF 11-12).

We conclude that the Examiner has set forth a prima facie case that claims 1 and 11 would have been obvious to the ordinary artisan in view of Nasir and Dixon. In *KSR*, the Supreme Court indicated that "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007). In the instant case, application of Nasir's method of detection of mycotoxins to the detection of aflatoxin is a predictable variation.

We are not persuaded by Appellants' argument that neither Dixon nor Nasir teach a "tracer comprising an aflatoxin oxime conjugated to a fluorophore" (App. Br. 3). We think that Appellants incorrectly characterize the logic of the combination of Nasir and Dixon in order to arrive at this conclusion. Nasir clearly teaches a tracer of mycotoxin conjugated to a

fluorophore label (FF 3). Dixon equally clearly teaches that aflatoxin is a mycotoxin of interest (FF 9) and that the only way in which aflatoxin B_1 can be conjugated to an entity (such as a fluorophore label) is by first forming an aflatoxin B_1-oxime (FF 11). Consequently, when the ordinary practitioner follows the guidance of Nasir and Dixon to fluorescently label aflatoxin as the mycotoxin tracer, Dixon shows that the oxime is required to successfully achieve the labeling (*see* FF 11-12).

It appears that Appellants argue that it is nonobvious to substitute a fluorophore label for a horseradish peroxidase label. However, Dixon expressly teaches the use of the enzymatic label for an ELISA assay (FF 10). Nasir teaches that in the improved fluorescence polarization assay, fluorescent label is used (FF 6). Since Nasir directly teaches that a fluorescent label is desirable and that fluorescence polarization is a superior method (FF 8), we conclude that there is significant motivation and reason to substitute a fluorescent label for the horseradish peroxidase label shown in Dixon.

While Appellants are correct that changing the label in Dixon to a fluorophore would change the operation of Dixon (App. Br. 5), the obviousness combination rests upon using the mycotoxin detection method of Nasir to detect the mycotoxin species, aflatoxin, and not to directly use the method of Dixon for the detection (*see* FF 1-12).

We reject Appellants' argument that Nasir teaches away from an aflatoxin oxime and that Nasir fails to teach a reasonable expectation of success (App. Br. 6). Like our appellate reviewing court, we "will not read into a reference a teaching away from a process where no such language

exists." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006). There is no language in Nasir which teaches away from aflatoxins, but rather, the discussion in Nasir expressly suggests that the method is suitable for all mycotoxins (*see* FF 1, 3-5).

We also do not think that Nasir and Dixon fail to provide a reasonable expectation of success for detection of aflatoxin. Dixon teaches that aflatoxin can be labelled and detected by antibody binding (FF 9-12). Nasir teaches that the fluorescence polarization method was successful with at least three different toxins (FF 7). These teachings would have provided a foundation for a reasonable expectation of success since it would be expected that if antibody detection of aflatoxin functions, the antibody based fluorescence polarization tracer method of Nasir would also function. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success . . . . For obviousness under § 103, all that is required is a reasonable expectation of success.").

While we have carefully considered the Nasir declaration, we find that the fact that Nasir was unable to label the aflatoxin until they found that aflatoxin oxime could be labeled (Nasir Declaration, ¶ 5-6) actually supports the obviousness rejection. Dixon teaches that "[s]ince aflatoxin B_1 possesses no reactive groups for conjugation, it was first converted to aflatoxin- B_1-carboxymethylamine (aflatoxin B_1-oxime)" (Dixon 4:66-68). Therefore, the the preponderance of the evidence on this record shows that the ordinary practitioner would have been taught by Dixon to form an aflatoxin B_1-oxime

in order to make a tracer for the fluorescence polarization method of Nasir (*see* FF 8-12).

We also reject Appellants' argument that "the Examiner has not identified any prior art teaching that an aflatoxin oxime conjugated to a fluorophore would still be able to bind to an antibody specific for aflatoxin" (App. Br. 8). In fact, the Examiner has cited Dixon, who shows that an antibody will detect aflatoxin conjugated to BSA (Dixon 7:51-53, table 1) and aflatoxin conjugated to horseradish peroxidase (Dixon 6:35-44). There is a reasonable expectation that if the much larger BSA and horseradish peroxidase molecules do not sterically hinder the antibody from binding the aflatoxin, the much smaller fluorophores will also not prevent antibody binding. *See In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) ("Obviousness does not require absolute predictability of success . . . . For obviousness under § 103, all that is required is a reasonable expectation of success.").

We also reject Appellants' argument that it is unpredictable whether binding will produce a detectable change in fluorescence polarization (see App. Br. 8). Appellants rely upon a statement in Nasir regarding the "propeller effect", in which binding occurs but little polarization shift is observed (App. Br. 8). When Nasir discusses the "propeller effect", Nasir not only mentions that the problem is due to long, flexible linkages, but expressly discusses how to solve the problem, noting that "[t]o attain the best results one must employ the shortest and most rigid linkage possible between the fluorophore and the ligand. In addition one must achieve a high quantum yield and appropriate fluorescence lifetime" (Nasir 180, col. 2).

Since Nasir teaches precisely how to solve the problem with the "propeller effect", Nasir supports a conclusion that there is at least a "reasonable expectation of success". This reasonable expectation of success is bolstered by Nasir's citation of prior art references that disclose that the fluorescence polarization method worked for multiple different toxins, as well as antibodies, hormones, cancer proteins, DNA, and carbohydrates (*see* Nasir 181-184).

Appellants also argue that an "obvious to try" rationale is employed by the Examiner (App. Br. 10). As the Supreme Court in *KSR* concluded:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product [is] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 127 S. Ct. at 1742. Based upon the teachings of Nasir and the strong motivation by Nasir to employ the fluorescence polarization method for detection of molecules of interest, particularly mycotoxins, and the teaching of Dixon that aflatoxin is a mycotoxin of interest, we conclude that it would have been more than obvious to try the application of the Nasir method to Dixon's aflatoxins. In fact, given the strong teaching by Dixon that aflatoxins are important mycotoxins in grain (FF 9-10) and the very strong suggestion by Nasir (FF 8) to apply fluorescence polarization to detect mycotoxins, we find that there is

express teaching, suggestion and motivation to obtain the instant invention.

We affirm the rejection of claims 1 and 11 as obvious over Nasir and Dixon. Claims 2-4, 8 and 12-18 fall with claims 1 and 11 as they were not separately argued.

35 U.S.C. § 103(a) rejection over Dixon, Nasir, and Michel

Claims 5-7 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Dixon, Nasir, and Michel.

The Examiner relies on the combination of Dixon and Nasir as discussed above. The Examiner relies on Michel to reach the limitations of claims 5-7, drawn to specific fluorescent labels, which ultimately depend from claim 1. We will affirm this rejection since Appellants do not separately argue these claims and rely upon overcoming the primary rejection of Dixon and Nasir, which was affirmed above.

35 U.S.C. § 103(a) rejection over Dixon, Nasir, and McMahon

Claims 9-10 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Dixon, Nasir, and McMahon.

The Examiner relies on the combination of Dixon and Nasir as discussed above. The Examiner relies on McMahon to reach the limitations of claims 9-10, drawn to forming standard curves, which ultimately depend from claim 1. We will affirm this rejection since Appellants do not separately argue these claims and rely upon overcoming the primary rejection of Dixon and Nasir, which was affirmed above.

CONCLUSION

In summary, we affirm the rejection of claims 1 and 11 under 35 U.S.C. § 103(a). Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejections of claims 2-4, 8 and 12-18 as these claims were not argued separately. We also affirm the rejections of claims 5-7 and 9-10 because Appellants have not rebutted the Examiner's prima facie case of obviousness.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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